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Preview

To Claim Growth Turf, mTOR Says SOD Off

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Maintaining redox balance in cancer cells is essential for tumor development and progression. In this issue of *Molecular Cell*, Tsang et al. (2018) identify an evolutionarily conserved mTORC1-dependent mechanism by which cancer cells control redox homeostasis in ischemic tumor microenvironment.

Cancer cells are characterized by an elevated rate of intracellular reactive oxygen species (ROS) production due to accelerated metabolism, oncogenic mutations, and adaptation to tumor microenvironments (i.e., hypoxia, infiltrating immune cells, and nutrient deprivation). The increase in ROS is co-opted by cancer cells to activate pro-tumorigenic signaling pathways necessary for their survival, proliferation, and metastasis (Reczek and Chandel, 2017). Such persistent pro-oxidative state, however, can cause oxidative stress-induced senescence and cell death. As a result, cancer cells increase their antioxidant capabilities, in part by activating the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) (DeNicola et al., 2011). In this issue of *Molecular Cell*, Tsang et al. (2018) show that cancer cells maintain redox homeostasis during nutrient deprivation through mechanistic target of rapamycin complex 1 (mTORC1)-mediated control of the antioxidant protein superoxide dismutase 1 (SOD1).

SOD1 is the primary cytosolic antioxidant protein against accumulation of superoxide ($\text{O}_2^\cdot$). The enzyme catalyzes rapid conversion of $\text{O}_2^\cdot$ into hydrogen peroxide ($\text{H}_2\text{O}_2$), maintaining a low concentration of intracellular $\text{O}_2^\cdot$. Accordingly, cancer cells display an increased SOD1 activity (Somwar et al., 2011). Protein kinase mTORC1 is the master regulator of cell growth and metabolism. In the presence of growth factors and amino acids, mTORC1 phosphorylates a myriad of proteins to promote anabolism while suppressing catabolic processes such as autophagy (Saxton and Sabatini, 2017). Inhibiting mTORC1 with the natural product rapamycin therefore diminishes cell growth and proliferation. Previously, a loss of SOD1 was shown to confer rapamycin resistance in yeast, suggesting that SOD1 is genetically connected to the mTORC1 signaling pathway (Neklesa and Davis, 2008). Building upon this observation, Tsang et al. (2018) discovered that both pharmacological and genetic inhibitions of mTORC1 result in enhanced SOD1 activity in yeast.

Tsang et al. (2018) systematically dissected the mechanism by which mTORC1 negatively affects SOD1 activity. Mass spectrometry analysis elicited that phosphorylation of serine-39 (S39) on SOD1 is sensitive to rapamycin. The authors subsequently generated SOD1 with phosphomimetic (S39D/E) or non-phosphorylatable (S39A) mutations. Testing the in situ phosphorylation of purified SOD1野生型 or SOD1S39A by mTORC1 further confirmed that mTORC1 phosphorylates SOD1 on S39. Comparing the SOD activities and $\text{O}_2^\cdot$ contents in yeast cells expressing SOD1野生型, SOD1S39A, or SOD1S39D/E showed that S39-phosphorylated SOD1 had reduced $\text{O}_2^\cdot$ scavenging activity. Importantly, the negative regulation of SOD1 by mTORC1 is conserved in human cancer cell lines. mTORC1 phosphorylates mammalian SOD1 on threonine-40 (T40), located at the same position as S39 of yeast SOD1, to reduce the SOD1 activity.

The mTORC1-SOD1 axis has important implications in redox balance of cancer cells under a changing nutritional environment. As tumor growth rates exceed vasculature growth rates, solid tumor cells frequently undergo deprivation of oxygen and nutrients. Such an ischemic condition increases production of ROS and suppresses mTORC1 signaling. Therefore, mTORC1 inhibition under ischemia can result in reduced T40-phosphorylation of SOD1 and increased SOD1 activity, thus allowing cancer cells to survive high levels of ischemia-induced ROS (Figure 1). Indeed, the reversible phosphorylation on T40 of SOD1 was found to be necessary for the regulation of SOD1 activity under ischemia. Furthermore, expression of SOD1T40E in cancer cells resulted in significantly increased cell death under ischemia, which was rescued by a SOD mimetic, TEMPO. Next, Tsang et al. (2018) investigated the effect of SOD1T40A or SOD1T40E expression in tumor spheroid culture and mouse xenografts. SOD1T40E attenuated the formation of tumor spheroids and xenografts, while SOD1T40A potentiated their establishment. Collectively, these results support that cancer cells maintain redox homeostasis in an ischemic environment via increasing SOD1 activity, mediated by mTORC1 inhibition. Interestingly, increasing the cytosolic oxidizing environment in mammalian cells has been shown to activate mTORC1 activity through unknown mechanisms (Sarbassov and Sabatini, 2005).

Due to its well-recognized pro-growth and proliferative functions, mTORC1 has been rigorously explored as a target for cancer therapy. Following encouraging initial clinical trials, inhibitors of mTORC1, known as rapalogs, were approved as anti-cancer agents. However, the overall outcome in patients on rapalogs has been equivocal (Laigan and Manning, 2016). The study by Tsang et al. (2018) suggests that mTORC1 inhibitors might help cancer cells to survive nutrient-deprived tumor microenvironments by promoting redox balance. Indeed, it will be of high interest to test whether the lack of efficacy of rapalogs in ischemic solid tumors, such as pancreatic cancer, is due to increasing antioxidant capacity. Previous studies indicate that...
limiting antioxidant capacity of Kras-driven lung cancer cells by disabling NRF2 or SOD1 diminishes tumorigenesis (DeNicola et al., 2011; Glasauer et al., 2014). Thus, targeting antioxidant proteins might increase the efficacy of rapalog as anti-cancer therapies.

Apart from its therapeutic potential, the study by Tsang et al. (2018) also leaves an intriguing question on cellular redox biology: why was mTORC1 suppression of SOD1 evolutionarily conserved? The authors hint that the mechanism in which mTORC1 inhibition activates SOD1 allows eukaryotic cells under nutrient deprivation to cope with the increased mitochondria-generated ROS. However, it is important to note that the inhibition of mTORC1 activates the cytoplasmic SOD1, yet not the mitochondrial SOD2. This indicates that the mTORC1-SOD1 regulation may not be just a reserved stress response. In recent years, increasing evidence has emphasized the significance of the localization of ROS: a moderate amount of ROS proximal to the targets of ROS-dependent signaling promotes cell growth and proliferation, while excessive levels of ROS dispersing throughout the intracellular space can cause oxidative stress-induced damage (Chandel and Tuveson, 2014). This model proposes two hypotheses: (1) in nutrient sufficiency, mTORC1 may inactivate SOD1 to increase surrounding cytosolic ROS concentration to potentiate ROS-dependent signaling, and (2) under nutrient deprivation, mTORC1 inhibition and the resulting increase in SOD1 activity may prevent cytotoxic ROS from accumulating to damaging levels, while allowing the elevated mitochondrial ROS to activate ROS-dependent signaling necessary for cells to adapt to starvation. It will be of interest to explore whether mTORC1 inactivates any other key antioxidant enzymes, such as peroxiredoxins, that are necessary to relay ROS-dependent signaling. The findings from Tsang et al. (2018) open the door for exciting investigations on the redox biology of cells under dynamic nutrient availability.

REFERENCES


